

Development of Pharmaceutical Compounds with Focus on Clinical Trials

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Today's agenda

- Introduction
- Your expectations
- Presentation
 - CV An van Es -Johansson
 - Bringing a compound to the patient – with focus on Clinical Trials
 - Coffee/Tea break
- Q&A



Your expectations



What are your expectations for those 2 hours with me ?



What are the specific questions you have regarding clinical trials that would be useful for your project?

My Working Experience

- M.D , physician –pediatrics Netherlands
- Pharmaceutical career : clinical development, business development, commercial, medical affairs, executive management
- Netherlands, Sweden, USA, Switzerland
- Big Pharma and biotech , HQ and affiliate
- Pharmacia, Eli Lilly, Roche, Active Biotech, Biovitrum, SOBI

Currently:

- CEO vanesconsulting AB
- Boardmember of Bioinvent and Alzecure
- Leadership Coach / Mentor



references

- <http://fda.com/>
- <http://www.ema.europa.eu/>
- <https://clinicaltrials.gov/>

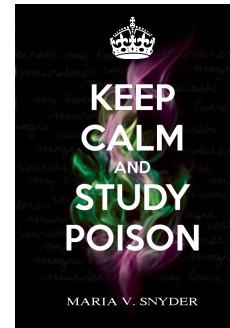


Pharma and Biotech - the arena



Pharma / Biotech -arena

- Complex!!!
- Costs!!!!!!!!!!!!!!
- Crisis!!!!
- Exciting and you never stop learning!



R&D “productivity crisis “ in pharma industry

- R&D costs are increasing while output decreasing
- Average costs of developing novel drug increases



Proposed solutions to "productivity crisis"

- Mergers & Acquisitions (M&A)
- In-licensing & alliances (extramural R&D)
- Increased use of CROs
- Biomarkers
- Smart and shorter development plans
- Translational medicine
- Increased marketing
- Cost reductions
-
-
-



There is no shortcut !

- Clinical data needed
- Risk benefit of a compound must be positive
- Value must be shown
- Real world data required 
- Regulatory approval
- Reimbursement

Data needed !!



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What is new ?

- Pricing and reimbursement
- Need for real world data
- Involvement of medical affairs
- Patient advocacy
- Regulatory strategies- pathways to take
- The classes of compounds- i.e immuno oncology
- Orphan drugs

What it is we want ?

Stakeholders:

- Patient
- Physician
- Pharmaceutical company
- Authorities
- Reimbursement/pricing system
- Investors



Wanted A New Pharmaceutical Product

- Novel treatment for an unmet medical need
 - or
- Better efficacy
- Better safety
- Better administration
- Better economy
 - or
- Me-too /biosimilars



What is important for the company ?

- First to market
- Competitor
- Time to market
- Cost
- Portfolio management: Risks - frontloading
- Pricing / reimbursement
- Medical need
- Package insert / label

Bringing a compound to the patient – with focus on Clinical Trials

What is Clinical Research?

“The controlled exposure of a selected population of humans to a pharmacological active product with the aim of testing an hypothesis”



Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that data and reported results are credible and accurate

and

that rights, integrity, and confidentiality of trial subjects are protected



Phases of Drug Research



From Laboratory to Patient

- Pre-Clinical Development:
 - Animal studies
- **Clinical Development = Studies in human beings**
 - Healthy volunteers & patients
 - Phases I to IV and PMS studies

Before Giving the Candidate Drug to Humans

- Pharmacology
 - Predicted exposure for intended effect
- Toxicology
 - Expected side-effects
 - Exposure at NOAEL levels
- Pharmacokinetics
 - Predicted metabolites and route of metabolism
 - Predicted PK variables
- Safety margin
 - Expected maximum tolerated dose and the expected effective dose in humans



Phases in Clinical Trials

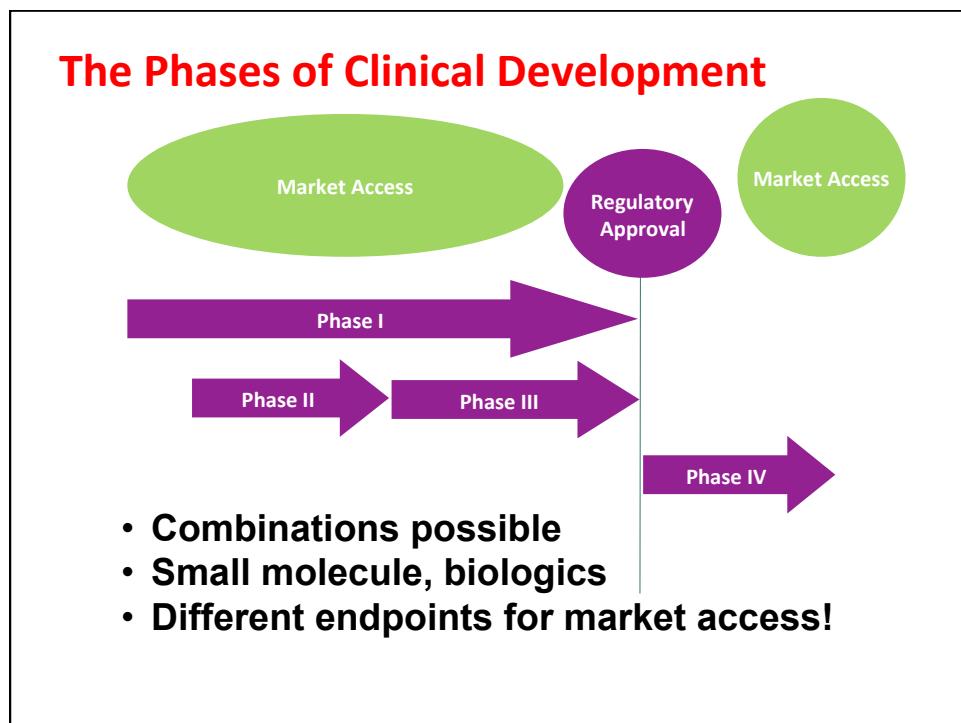
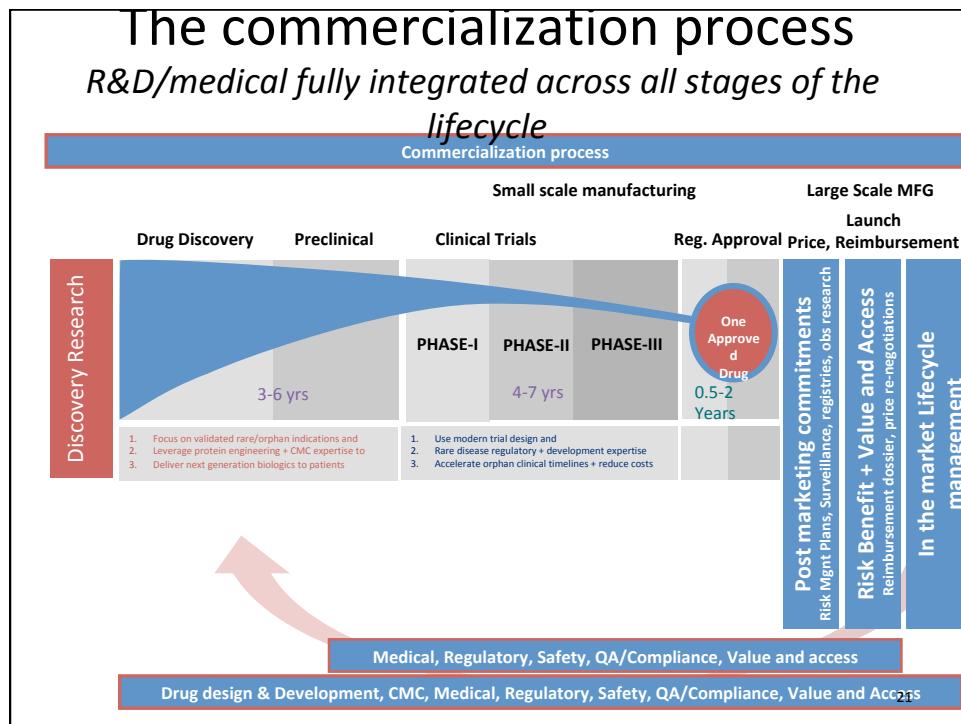
In [Phase I trials](#), we test an experimental drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects

In [Phase II trials](#), the experimental study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.



In [Phase III trials](#), the experimental study drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

In [Phase IV trials](#), post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.



Types of clinical trials

Treatment trials

test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.

Prevention trials

look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes.

Diagnostic trials

are conducted to find better tests or procedures for diagnosing a particular disease or condition.

Screening trials

test the best way to detect certain diseases or health conditions.

Quality of Life trials

explore ways to improve comfort and the quality of life for individuals with a chronic illness

Clinical Development Plan-1

- Pivotal studies for the registration file
- 2 confirming Phase 3 studies ,placebo controlled or with comparator
- Relevant-comparator,
- Targetting the right patients
- Pediatric investigational plan (P.I.P)
- Working with Key Opinion Leaders 
- Fast and smart
- Always ethical



Clinical Development Plan-2

- Combination of different phases:PI/II or PII/III
- Directly into patients
- Combination of drugs -Immuno-oncology
- Few patients- Orphan drugs
- Market access-early studies to prove value in addition to safety and efficacy



Coffee! Tea!!



Clinical trials designed to show :
Safety in Humans
Efficacy in Humans

Necessary to document that it :

- is this safe to give to humans
- gives the intended effect in humans

**The compound MUST have a positive benefit/
risk profile!!**

Clinical trials

Q&A



- Define all your own questions about clinical trials for your project

Clinical Trials

Open label
Double blind
Placebo controlled
Comparator
Cross-over
Parallel arms
Investigator sponsored study
Interventional study
Non-interventional study



Target Product Profile

working tool leading to the Package Insert

- A tool in the development of drugs
- Set up the criteria you want for your drug and then work backwards
- What do you need to document in phase III to get the "labeling" you need?
- What do you need to achieve in phase IIb?
- What do you need to achieve in phase IIA?

Market Access

patients get access to the drugs they need

- Biggest change in clinical development in last 5-10 years
- In Europe very decentralised process
- Value
- Comparator
- Health outcome data –real world data
- Pricing and reimbursement

Sponsor

Definition:

an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.

Investigator

Definition:

A person responsible for the conduct of the clinical trial at a trial site.

If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team.



Study subjects

- Healthy volunteers
 - Male /female
 - Patients
 - Subgroups
 - Elderly people
 - Children
 - Asians/African/Hispanic/Caucasian
-
- In/exclusion criteria
 - Patient informed consent
 - Own free will



Definition:

An individual who participates in a clinical trial, either as recipient of the investigational drug or as a control.

A subject may either be a patient or an healthy volunteer

Endpoints

- Efficacy endpoints
- Safety endpoints
- Primary endpoints
- Secondary endpoints
- Tertiary endpoints/exploratory endpoints, etc., etc.
- Compository endpoints



What to study ?

- Active compound
- Comparator
- Placebo



Contract Research Organisation

CRO activities:

- Monitoring + data retrieval
- Pharmaco-economic assistance
- Medical writing
- Statistics
- Site selections & management
- Protocol + CRF design
- Development planning
- Feasibility
- Strategic input

At the studysite

- Feasibility
- Studysite
- Studyteam
- Principle investigator
- Studynurse/ Study coordinator
- Insurance
- Ethical approval
- Contracts/ financial agreements
- Per patient fee

Inv. sites are:

- used by sponsors, CROs
 - recruit and enroll patients
 - Responsible for the medical care
 - report data accurately
 - ensure compliance with regulatory guidelines

Regulatory Authorities

- USA: FDA
- Europe: EMA
- Local country authorities, e.g. MPA = Sweden
- IRB (USA)
- Ethical committees (EU)
- Documentation
 - CTA, IND, NDA, IMPD, ICF, IB, Studyprotocol, amendment, reports, scientific Advice, Adverse events, Pharmacovigilance,
 - Preclinical documentation, pharmacology, formulation, etc., etc.
 - Inspections, audits

Approval

- Approval = Market authorization
- Fast track approval
- Conditional approval
- Post Marketing Commitments



Career in clinical trials?

- Monitor –CRA , CRM
- Project leader
- Medical writer
- Statistician
- Toxicologist
- Data entry
- Medical experts
- Safety experts
- Market access



Q & A



Contact details

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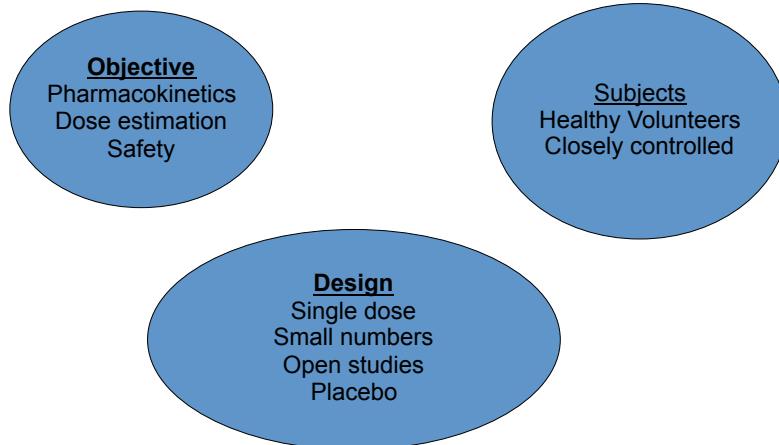
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Back-up slides



First Exposure in humans Phase I Unit

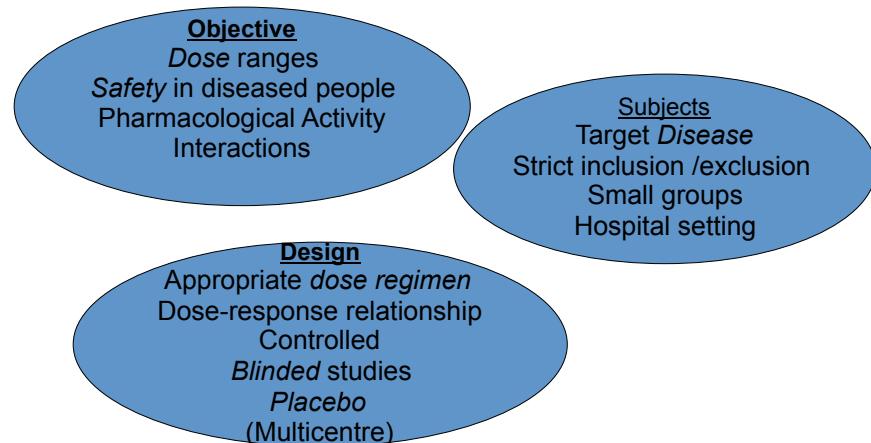


Phase I (Human Pharmacology)

A number of studies in healthy volunteers, studying

- Single- and multiple-dose pharmacokinetics
- Assess safety and tolerability
- Define/describe pharmacokinetics and pharmacodynamics
- Food effects
- Dose proportionality
- Drug metabolism
- Interaction studies
- Special populations (elderly, children, renal and hepatic failure)

Phase II Trials -therapeutic pilot studies



Phase II (Therapeutic Exploratory)

- Explore use for the targeted indication
Estimate doses for subsequent studies
- Surrogate end-points
 - Phase IIa – Proof-of-Concept
 - Phase IIb – Dose-finding
- Provide basis for confirmatory study design,
endpoints and methodologies

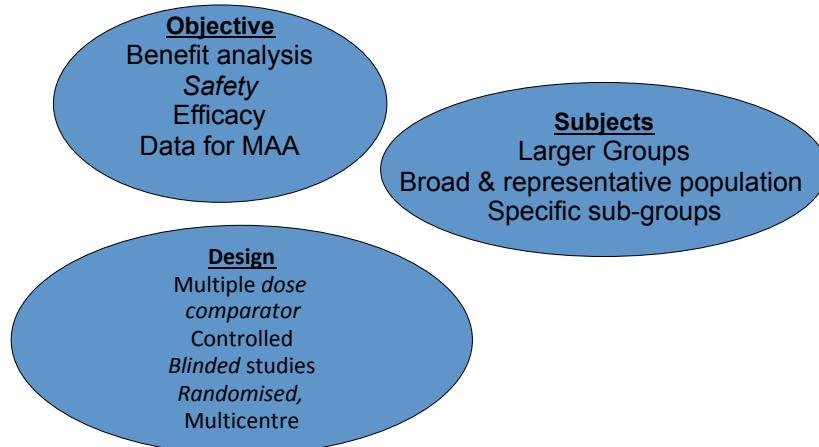
Phase IIa - Proof-of-Concept (POC) Summary

- Primary objective: to document the effect in humans
- Patients with targeted disease, however limitations in population (e.g. exclusion of fertile women)
- Limited number of dose groups and dosing frequency
- Toxicological documentation to allow treatment during 4 weeks
50 to 150 patients

Phase IIb – Dose-finding Summary

- Primary objective: to document lowest efficacious dose
- Patients with targeted disease
100 to 300 patients
- Show efficacy in patients over longer period with different doses

Phase III



Phase III (Therapeutic Confirmatory)

- Document basis for assessing the benefit/risk relationship with end-points acceptable to regulatory authorities

Pivotal studies

Phase III Summary

- Confirm efficacy over longer time with dose determined in phase II
- Establish safety profile (guidelines requirements)
- Patient population reflects clinical reality
- Placebo or market leader as comparator
- Outcome data and/or health economy

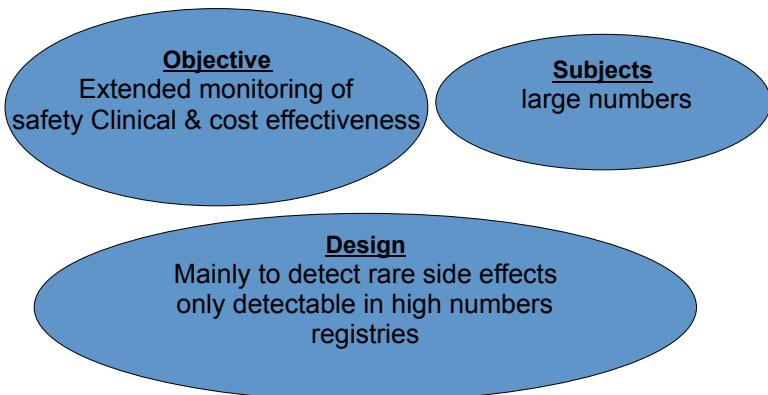
Phase IV MAA granted - on the market

Objective
Immediately post-launch
More safety & efficacy data
Highlight rare side-effects

Subjects
Cohort groups
Inclusion is more relaxed

Design
Multiple dose
Controlled
Randomised
Blinded/open studies
Comparative in some cases
Multicentre

PMS studies – real use situations



Phase IV – Post-marketing studies Summary

- Refine understanding of benefit/risk relationship in general or special populations
- Identify less common adverse reactions
- Refine the dosing recommendation
- Compliance
- Secure marketshare
- Requirements from the authority to follow use of the compound